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APPLICATION NO.	FILING DATE	PERSON NAMED INVENTOR	ADDRESS OF INVENTOR	ATTORNEY'S OFFICE NO.
09 768,661	01 23 2001	J. Richard Sportsman	1111 18101	1 80

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EXAMINER

NICHOLS, CHRISTOPHER J

ARTICLE	PAPER NUMBER
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2647

DATE MAILED 04 02 2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/768,661

Applicant(s)

SPORTSMAN ET AL.

Examiner

Christopher Nichols, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 February 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 36-57 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 36-57 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 January 2001 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2, 3.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election *without traverse* of Group VI (claims 29-30) in Paper No. 5 (3 February 2003) is acknowledged.

Status of Application, Amendments, and/or Claims

2. The Preliminary Amendment of 3 February 2003 (Paper No. 5) has been entered in full. Claims 1-35 have been cancelled. Claims 36-57 are under examination

Information Disclosure Statement

3. The information disclosure statement filed 8 May 2002 (Paper No. 3) fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because citation "4-344464" is not in the English language. This Japanese document (4-344464) has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Drawings

4. The drawings are objected to because Figures 7, 8, and 9 have two components each. These should contain reference to each individual component of the figures such as "Figure 7A

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and 7B", "Figure 8A and 8B", and "Figure 9A and 9B" in the "Brief Description of the Drawings" as done in the figure legend for Figure 4 (pp. 14). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims **36-57** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of measuring the generation or consumption of cAMP and cGMP by adenylyl cyclase and G-proteins respectively in the presence and absence of test compounds, does not reasonably provide enablement for any other enzymes which may consume or generate cyclic nucleotides or other natural or non-naturally occurring cyclic nucleotides or the performance of the assay *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.
6. Claims 36-57 are directed to a method for identifying a compound as a modulator of a reaction that generates or consumes a cyclic nucleotide. Said claims are drawn very broadly to methods of cells *in vitro* and *in vivo*. The use of *in vitro* systems as support for *in vivo* methods.

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the *in vitro* system as presented in the instant application is not predicative of an *in vivo* method.

The specification teaches a method of using the claimed method to identify a compound as a modulator of a reaction that generates or consumes a cyclic nucleotide in cells *in vitro*.

7. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of identification methods *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo*, such a disclosure would not be considered enabling since the state of modulating compounds is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

- a. The breadth of the claims;
- b. The nature of the invention;
- c. The state of the prior art;
- d. The level of one of ordinary skill;
- e. The level of predictability in the art;
- f. The amount of direction provided by the inventor;
- g. The existence of working examples; and
- h. The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

8. The following references are cited herein to illustrate the state of the art of cyclic nucleotide reactions and assays thereof.

9. Allen et al. [(February 2002) "A Homogeneous High Throughput Nonradioactive Method for Measurement of Functional Activity of G_s-Coupled Receptors in Membranes." Journal of Biomolecular Screening 7(1): 35-44] teach that existing screens for binding agents of serpentine

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or 7-transmembrane receptors (including G-protein coupled receptors and adenylyl cyclase) have four hurdles (pp. 38):

- i. "Ligand binding studies fail to distinguish agonism from antagonism
- j. Ligand binding screens may miss high-intrinsic-efficacy agonists that have low affinity
- k. Antagonists have been demonstrated that are active in functional screens but no in ligand binding screens
- l. Binding assays generally require high-receptor-expression and high-affinity ligands, which may not be available for novel receptors."

While it is acknowledged that the current invention is drawn to a method of identifying modulators, the proposed modulators must first bind the target enzyme and hence the instant application must overcome the above listed hurdles. Further Allen et al. teaches that it is important for assays used in screening are resistant to both vehicle effects and nonspecific effects of compounds. Particularly the effects of compounds on light intensity either because of autofluorescence or light scattering. Both effects can interfere with polarization measurements and may adversely affect control and test measurements (pp. 42).

10. Prystay et al. [(April 2002) "Homogenous Cell-Based Fluorescence Polarization Assay for the Direct Detection of cAMP." Journal of Biomolecular Screening 6(2): 75-82] teaches that colored compounds may interfere with polarization assay performance by either quenching or contributing to the fluorescent signal given off by a fluorescein-labeled cAMP. This is of particular significance since a library of compounds used to screen for modulators may contain numerous colored compounds which have unpredictable effects on the polarization signal

detection. For instance, Prystay et al. found that tartrazine (a bright yellow dye) increased the fluorescein-ligand fluorescence intensity while Chicago Sky Blue absorbed the assay fluorescence (pp. 82). These complications must be taken into consideration and addressed by a skilled artisan when using the claimed invention.

11. Finally, Huang et al. [(June 2002) "A Fluorescence Polarization Assay for Cyclic Nucleotide Phosphodiesterases." Journal of Biomolecular Screening 7(3): 215-222] teaches a method similar to the instant invention. While enabling for an *in vitro* method wherein the cyclic nucleotides are cAMP or cGMP does not provide guidance for *in vivo* assays or use of other cyclic nucleotides.

12. The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* identification of a compound as a modulator of a reaction that generates or consumes a cAMP or cGMP, as exemplified in the references above.

13. Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the identification of a modulating compound *in vitro* as being correlative or representative of the successful *in vivo* identification of a compound as a modulator of a reaction that generates or consumes a cyclic nucleotide.

14. Regarding identification of a compound as a modulator of a reaction that generates or consumes a cyclic nucleotide, the art recognizes that "a reaction that generates or consumes a cyclic nucleotide" can pertain to any number of enzymes including but not limited to adenylyl cyclase and guanylyl cyclase. Due to the large quantity of experimentation necessary to identify all the applicable reactions that generates or consumes a cyclic nucleotide, the lack of

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direction/guidance presented in the specification regarding synthesizing, screening, and evaluating all applicable modulators of reactions that generates or consumes a cyclic nucleotide, the absence of working examples directed to known modulators of reactions that generates or consumes a cyclic nucleotide, the complex nature of the invention, the unpredictability of the effects of modulators of reactions that generates or consumes a cyclic nucleotide on cells and/or patients, and the breadth of the claims which fail to recite limitations for what constitutes an applicable modulator of reactions that generates or consumes a cyclic nucleotide, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

15. Claims 36 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

16. The term "modulator" in claims 36 and 48 is a relative term which renders the claim indefinite. The term "modulator" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. US 5225543 [(6 July 1993) Eppler et al. (IDS)] teaches that "modulators" of reactions that generate or consume a cyclic nucleotide can be growth factors, neurotransmitters, releasing factors, or circulating hormones. The modulating compound may inhibit, increase, decrease, or bind to the enzyme involved in the reaction.

Summary

17. Claims 36-57 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Hummer

CJN
March 24, 2003